OCULAR MORBIDITY IN BONE MARROW AND PERIPHERAL BLOOD STEM CELL TRANSPLANT RECIPIENTS

OCULAR MORBIDITY IN BONE MARROW AND PERIPHERAL BLOOD STEM CELL TRANSPLANT RECIPIENTS

A dissertation submitted in partial fulfillment of the MS Branch III (Ophthalmology) examination of the Tamil Nadu Dr MGR Medical University to be held in March 2007

DECLARATION

I hereby declare that the investigations that form the subject matter of this thesis was carried out by me under the guidance of Dr. Pushpa Jacob, Professor of Ophthalmology, Christian Medical College, Vellore. This has not been submitted in any other university in part or in full.

Dr. Anupriya Arthur,

Department of Ophthalmology,

Schell Eye Hospital,

Christian Medical College, Vellore

Date: 31/8/2004

Place: Vellore

CERTIFICATE

This is to certify that this dissertation entitled "**Ocular morbidity in post bone marrow and peripheral blood stem cell transplant recipients**" is bonafide work done by Dr Anupriya Arthur in partial fulfillment of the rules and regulations for M.S.Branch III (Ophthalmology) examination of the Tamilnadu Dr MGR Medical University, Chennai, to be held in March 2007.

Dr Pushpa Jacob,
Professor,
Dissertation Guide,
Department of Ophthalmology,
Christian Medical College, Vellore.

Dr Sharada David
Professor & Head of the Dept
Department of Ophthalmology
Christian Medical College, Vellore.

Date :31/8/2006

Place :Vellore

Acknowledgement

I would like to express my deep sense of gratitude to my chief guide Dr. Pushpa Jacob, Professor Department of Ophthalmology for generating a novel topic for this dissertation and for the all the timely advice and much needed help.

I am especially grateful to the Department of Haematology especially Dr Mammen Chandy, Dr Alok Srivastav, Dr Auro and Dr Vikram for all the help extended for this study.

My sincere thanks to Dr Renu Raju, Dr Andrew Braganza and Dr Sharada David for their valuable support.

My sincere gratitude to Mr. Deenadayalan our Librarian, Mr. Able, Mr. Maydinaselvam and Mr Vishwanathan for all the help rendered. I also take this opportunity to thank the MRD staff especially Mr Rajasheker, Mr Sudhakar and Mr Albert for all their help.

I sincerely thank all my friends and colleagues for their support

To all the patients who were willing to come for the study a big Thank You.

Anu

CONTENTS

INTRODUCTION

The first successful transplantation of allogenic haematopoietic cells was performed in 1968 in three children with congenital immune deficiency.[1] Since then thousands of patients have received haematopoietic stem cell transplantation. Bone marrow transplantation has now become the treatment of choice for a wide variety of hematological and non hematological disorders such as aplastic anemia, hematological malignancies, transfusion dependent congenital anemias and some metabolic diseases.

The source of stem cells can be from bone marrow, peripheral blood or cord blood.

BMT uses ablation of the patient's own bone marrow with cytoreductive chemotherapeutic agents and with total body irradiation followed by transplantation of the donor marrow to reconstitute the patient's hematologic function.[2] The eyes are generally not shielded during total body irradiation because they are a potential site of leukaemia relapse. Subsequently the patient has to be maintained on a prolonged immunosuppressive regimen to prevent rejection of the transplanted bone marrow.

In general haematopoietic stem cell transplant can be classified into 3 different types[3]

1. Allogenic transplant – donor marrow is harvested from HLA compatible donor
2. Syngenic transplant – donor marrow is harvested from HLA compatible monozygotic twin

3. Autologous transplant - patients own bone marrow is harvested prior to induction therapy and later restored after chemotherapy and total body irradiation has been completed.

Complications following BMT are not uncommon and involve various organs like lungs, GIT and the eye. The underlying causes are multifactorial.[2] These includes side effects of the preparative regimens such as high dose chemotherapy, steroid treatment and irradiation as well as graft versus host reaction.[4] The major systemic complications post transplantation are infections and graft versus host disease (GVHD) which can be acute or chronic. In GVHD the lymphocytes of the immunocompetent donor mount an immunological attack on the immunoincompetent host. Two distinct clinical syndromes of GVHD have been described, acute and chronic. Acute GVHD clinically presents within the first 100 days of transplantation as an acute exanthematous dermatitis, enteritis and hepatitis. In contrast chronic GVHD occurs later than 100 days. It resembles an autoimmune illness with scleroderma like involvement of the skin, dacryoadenitis, chronic liver dysfunction and profound immunodeficiency[2].

Ocular complications following BMT are common. The most common anterior segment complications are keratoconjunctivitis sicca, cataract and corneal ulcers. Posterior segment complications include vitreous hemorrhage, microvascular retinopathy, optic disc edema and fungal and viral retinitis. Infectious and hemorrhagic lesions can occur as a consequence of transient pancytopenia immediately following the transplant. The infectious complications include fungal endophthalmitis, infectious keratitis and

herpes zoster ophthalmicus. Hemorrhagic complications include subconjunctival hemorrhage and intraretinal and vitreous hemorrhage.[5]

Ocular complications are common, but they are often underreported and under diagnosed due to lack of awareness and because of other life threatening systemic complications that overshadow them. Even though most of these complications do not lead to blindness, they can lead to significant ocular morbidity if appropriate treatment is not promptly initiated.

There is no data in this field from the Indian subcontinent. This study aims to evaluate the presence of ocular morbidity in patients undergoing bone marrow transplantation and peripheral blood stem cell transplantation.

AIMS

To document the presence of ocular morbidity in patients on follow up after bone marrow or peripheral blood stem cell transplantation.

LITERATURE REVIEW

Allogenic bone marrow transplant is an important treatment option for both malignant and non malignant neoplasms of the bone marrow including leukaemias, lymphomas and severe aplastic anemia.[5]

Allogenic bone marrow transplantation (BMT) from an HLA-identical sibling is effective therapy for patients with bone marrow failure states and those with hematologic malignancies. However, only a minority of them will have an HLA-identical sibling donor. Unrelated matched or partially mismatched donors have been used successfully for patients lacking a related donor. Even though results with allogenic transplants using unrelated donors are encouraging, the incidence of complications including graft-versus-host disease (GVHD) and graft rejection or late graft failure is increased compared to HLA identical sibling transplants. The combination of cyclophosphamide and total body irradiation (TBI) has been used as an effective preparative regimen for allogenic transplants.[6] By this **conditioning regimen** the patients own bone marrow is destroyed. The purpose of the regimen is to eradicate all malignant cells and to suppress the host immune response. The donor marrow is then transplanted to repopulate the host bone marrow thereby re-establishing the haematologic function.

Depending on the source of the stem cells, transplantation include peripheral blood stem cell transplant, bone marrow transplantation and cord blood transplantation **The technique of BMT** consists of sterile removal of bone marrow from the iliac crest.[7] The marrow is intravenously infused into the recipient. Subsequently the patients are maintained on a prolonged immunosuppression to prevent rejection of the transplanted bone marrow cells.

In Peripheral blood stem cell transplantation a variety of mobilization techniques are used to increase the number of stem and progenitor cells circulating in the peripheral blood.[8] After mobilization, an apheresis machine collects the cells. After venous blood is collected and processed through the apheresis machine, the nontargeted components are returned to the patient.

In general bone marrow transplant can be classified into 3 different types[3]

4. **Allogenic transplant** - using an HLA compatible donor
5. **Syngenic transplant** - HLA compatible monozygotic twin is the donor
6. **Autologous transplant** - Patients own bone marrow is used. Prior to induction therapy patients marrow is harvested and later restored after chemotherapy and TBI has been completed.

Subsequently following allogenic transplantation the patient has to be maintained on a prolonged immunosuppressive regimen to prevent rejection of the transplanted bone marrow.

The major systemic complications post transplantation are infections and graft versus host disease.[9]

Graft versus host disease:

In graft versus host disease lymphocytes of the immunocompetent donor mount an immunologic attack on the now immunoincompetent host.[9] GVHD can be of two types acute and chronic.

Acute GVHD occurs within hundred days of transplantation in 30 to 60% of histocompatible sibling matched allografts. Mortality directly or indirectly due to acute GVHD may reach 50%. It classically presents as an acute exanthematous dermatitis, enteritis or hepatitis.[11]

Chronic GVHD develops in 30 to 50% of patients approximately 3 to 6 months after transplantation. It resembles an autoimmune illness with scleroderma like involvement of the skin, dacryoadenitis, chronic liver dysfunction and profound immunodeficiency with recurrent bacterial infections.[12] Those at risk for chronic GVHD include older patients and those with previous acute GVHD.

Peripheral blood haematopoietic stem cell transplants have been shown to result in more rapid engraftment than standard bone marrow transplants and have better 2 year survival rates.[10] But the rapid engraftment by itself in these transplant recipients

could lead to chronic GVHD and late systemic fungal and cytomegalovirus (CMV) infection.[10]

Pathogenesis:

Recognition of allogenic difference by competent immunogenic cells is the central event of GVHD.[9] GVHD occurs when immunocompetent transplanted marrow cells target antigens on the surface of recipient cells.

The first step in the development of GVHD is the **recognition** of host peptides by allotransplanted immune cells. A co stimulatory signal determines whether peptide recognition will lead to full or partial **activation** of an immunologic response.[13] **Secretion** of interleukin 2 (IL 2) leads to clonal expansion and proliferation of T cells. T cells and monocytes in turn release cytokines, TNF alpha and interferon gamma which recruit other T cells and natural killer cells.[14] In support of this both CD4 and CD8 lymphocytes can be found in GVHD lesions.

Dysregulation of the intrinsic cytokine network is a primary cause for the induction and maintancence of GVHD.[15]

Antin and Ferrara proposed that GVHD after allogenic BMT may be pathophysiologically characterized as a cytokine storm comprising three steps.[16] The initial step involves damage to the host tissue – skin, intestinal mucosa and liver caused by radiation and / or chemotherapy during the conditioning regimen leading to the

production of proinflammatory cytokines such as IL-1 and tumor necrosis factor alpha (TNF α). These in turn cause increased expression of HLA alloantigens and adhesion molecules on the surface of the host cells leading to activation and proliferation of mature donor T cells.

> In the acute or suppurative form of GVHD the principal T cell response is a helper T cell type 1 or an inflammatory response with production of IL2 and interferon alpha. These cytokines activate additional donor and residual host mononuclear cells and macrophages resulting in the secretion of IL1, TNF alpha and other cytokines and consequent amplification of the pathogenic cycle.

The chronic or stimulatory form of GVHD is characterized by increased immunoglobulins E synthesis and exaggerated lymphoproliferative production of IL4 and IL10 by helper T cells.

One approach taken to prevent the cytokine storm after allogenic BMT has been to deplete donor T cells from the graft before infusion into the host. Although this maneuver reduces the risk of subsequent development of GVHD it concomitantly impairs the engraftment of donor cells and increases the risk of relapse of malignancy. The latter phenomenon has been attributed to the depletion of the cell mediating the so called graft vs host reaction. The exact identity of these cells and their relationship to those mediating GVHD remains unclear.

Systemic manifestations:

GVHD is manifested primarily by symptoms and signs associated with skin, GIT and liver.[17] Cells reacting in an autoimmune fashion produce abnormal pattern of

cytokines which stimulate collagen production by fibroblasts. Both the B and T subsets of lymphocytes are altered qualitatively and quantitatively. However in severe GVHD bone marrow suppression may also occur. 60 to 80% of patients with acute GVHD will go on to develop chronic GVHD.[24] 25 % of those who do not have acute GVHD go on to develop chronic GVHD. Acute and chronic GVHD differs in its distribution of target organs and its clinical presentation.[18] Acute GVHD primarily affects the skin ,liver and GIT.[19]

Skin

Mild **acute** GVHD of the skin presents as erythema and the severity increases as the percentage of body surface area involved increases. In severe cutaneous acute GVHD there is bulla formation and desquamation. The pathogenesis is immune mediated attack on the skin epithelium by the donor lymphocytes.

Staging of skin involvement in acute GVHD

Stage 1 - less than 25% of total body surface area

Stage 2 - 25-50% of total body surface area

Stage 3 - greater than 50% of total body surface area

Stage 4 - bulla formation

More than 90% of patients with **chronic** GVHD have cutaneous abnormality.[20] Two predominant forms have been noted. One type is similar to lichen planus and the other resembles morphea.[21]

Liver

The organ next commonly affected by **acute** GVHD is the liver. The earliest abnormality is a rise in conjugated bilirubin and the alkaline phosphatase level reflecting underlying damage to the bile canaliculi. In **chronic** GVHD cholestasis is common.

GIT

Gastrointestinal tract is the third most commonly affected organ. It can be the most severe and is refractory to treatment. Symptoms include abdominal cramps and diarrhea, which may exceed ten liters per day and may result in severe dehydration. The diarrhea is seedy representing epithelial desquamation. Severe cases can have haematochezia. In **chronic** GVHD enteritis is uncommon. [20] Secretory diarrhea and fat malabsorption can occur.

Clinical staging of liver involvement is based on elevation of liver enzymes and bilirubin levels, while staging of GIT involvement is based on volume of diarrhea.

Treatment for systemic GVHD

Corticosteroids are the mainstay of therapy. Dosing is titrated according to the grade and severity of GVHD. It can range from one milligramme per kilogramme to

three milligramme per kilogramme per day.[22] Cyclosporine can also be used as primary therapy. Thalidomide has also been described.[23] Chronic GVHD if left untreated has an overall survival rate of 18% .[24]

Prevention of GVHD

One approach to prevent GVHD is to use antibodies that recognize antigens expressed on T cells. With this acute GVHD develops in less than 10% of patients but engraftment fails to achieve in 20%. Another approach is induction of post transplant immunosuppression with a combination of Methorexate and Cyclosporine.[25] With this incidence of GVHD has decreased from 50% to 20%.

Ocular Morbidity in Bone Marrow Transplantation

. Ocular morbidity is divided into two groups, depending on whether they occur in the acute phase or in the chronic phase.[26]

Acute phase complications:

1. Pseudomembranous conjunctivitis
2. Corneal ulcer
3. Episcleritis
4. Secondary choroidal detachment
5. Secondary glaucoma
6. Cytarabine induced keratitis
7. Herpes simplex virus infections

Chronic phase complications:

1. Dry eye
2. Meibomian gland dysfunction
3. Retinal hemorrhages
4. Aseptic conjunctivitis
5. Lagophthalmos
6. Corneal thinning
7. Corneal melting
8. Nasolacrimal duct obstruction
9. Prolonged corneal ulcer
10. Calcareous corneal degeneration
11. Optic disc edema
12. Cotton wool spots
13. Cataract

Acute Phase complications

Pseudomembranous conjunctivitis can occur secondary to acute GVHD. Conjunctival involvement is a marker for severe systemic involvement in GVHD. Conjunctival GVHD presenting with pseudomembrane formation results from loss of the conjunctival epithelium.[26]

Herpes Simplex keratitis although rare can occur as an infectious complication. Approximately 80% of herpes infection involve the oral cavity. In the eye it tends to

occur early, usually during the first month after SCT and is due to the result of the virus reactivation.

Cytarabine induced keratitis is due to high concentration of the drug in the tears It is usually noted four to seven days after commencement of therapy with Cytosine arabinoside.[27] It presents with symptoms of foreign body sensation, photophobia and blurred vision. The conjunctiva shows hyperaemia and chemosis. Corneal changes varies from refractile epithelial microcysts, central punctate erosions, sub epithelial opacities and mild stromal oedema. Topical steroids are the treatment of choice. Steroids are given till all the symptoms and signs disappear.

Chronic phase complications :

Meibomian gland dysfunction is frequently associated with severe dry eye and is related to chronic GVHD. The evaluation of meibomian gland dysfunction is helpful for the diagnosis of dry eye.[28]

Recurrent corneal perforation and acute calcareous degeneration that can be recalcitrant to medical and surgical treatment can occur in chronic GVHD as a complication of keratoconjunctivitis sicca.[29]

Cataract after SCT usually develops within 3 to 5 years. Cataract genesis is caused by a combination of pretreatment with antimitotic agents, exposure to radiation

during the conditioning process and prolonged use of systemic steroids. Cataract is usually posterior subcapsular.

Lagophthalmos**,** corneal thinning, corneal melting, nasolacrimal duct block and chronic dacrocystitis can be seen as late complications. Acute anterior uveitis can develop for up to 20 months after transplantation.

Retinal hemorrhages is related to GVHD, vasculopathy, CMV retinitis or recurrence of leukemic disease.

Anterior segment complications

The most common anterior segment complications are keratoconjunctivitis sicca, cataract. These are more common in patients in patients with GVHD[26] and is described in detail later.

Posterior segment complications

The common posterior segment complications are vitreous hemorrhage, microvascular retinopathy, optic disc edema and fungal and viral retinitis.

Retinal complications of bone marrow transplantation

Posterior segment complications are less frequently encountered, but they can have significant visual consequences and implications. About 12% of patients can develop posterior segment complications.[30]

They are of 3 types[31]

1. Micro vascular retinopathy
2. Infection
3. Hematological complications

Bone Marrow Transplant retinopathy was first reported in 1983. It usually occurs within 6 months of BMT. It can occur as early as 3 months or as late as 62 months after BMT. Diabetes can facilitate the development of BMT retinopathy by contributing to the ischemic microvasculopathy. There are no known predictors like age, gender and race for this complication.

Clinical features of BMT Retinopathy

Patients present with decreased visual acuity, field deficit or both. Retinal findings are typically bilateral and symmetrical. Clinical findings include multiple cotton wool spots, telangiectasias, microaneurysms, macular edema, hard exudates and retinal hemorrhages.

Occlusive microvascular retinopathy has been described after BMT with retinal oedema, hemorrhage, soft exudates and neovascularisation in the posterior pole and peripheral fundus. It regresses and cicatrises with oral steroids. The visual prognosis depends on the foveal involvement of the retinopathy.[32] ***Fluorescein angiogram*** often reveals capillary non perfusion and dropouts. Intraretinal microvascular abnormality,

microaneurysm and fluorescein leakage around the fovea consistent with macular edema can be seen.

Bilateral optic disc oedema may also be present.[33,34] This can be due to microvascular retinopathy or to cyclosporine induced neurotoxicity.

Pathogenesis: The exact cause for BMT retinopathy is yet to be ascertained. Cyclosporine toxicity, total body irradiation and conditioning chemotherapy have been implicated.

Cyclosporine is a potent immunosuppressive agent. It can cause endothelial cell injury. Other side effects are nephrotoxicity, hypertension, seizures, encephalopathy, cortical blindness, cerebellar and spinal syndromes and raised intracranial tension. But it has not been demonstrated to cause BMT retinopathy in autologous or syngenic bone marrow recipients or in renal transplant patients. Drugs such as Cisplatin, Carmustin and Cyclophosphamide can cause ocular side effects including papillodema, optic neuritis, visual field defects and cortical blindness. Cyclosporine induced retinal toxic blindness can occur.[35]

TBI damages the retinal microvasculature and may lead to ischemic vasculopathy. Modifying factors such as total dose of irradiation and the time interval between radiation and bone marrow ablation are important.[36] The incidence and severity of BMT retinopathy correlate with high total body irradiation and a short time interval between

radiation and BMT. Therefore irradiation is not the sole factor but it appears to be another contributory factor in the development of BMT retinopathy.

BMT retinopathy and radiation retinopathy have similar clinical features including multiple cotton wool spots, telangiectasia, microaneurysms, macular edema, hard exudates and retinal hemorrhages.

But there are definite differences between the two[37]

1) BMT retinopathy is generally reversible where as radiation retinopathy is progressive. In fact BMT retinopathy does not progress beyond the ischemic microvascular stage.

2) Radiation retinopathy is often refractory to treatment.

3) BMT retinopathy is usually observed within 6 months of BMT but radiation retinopathy manifest approximately 18 months after the treatment

Patients with BMT retinopathy usually have a good prognosis – the retinopathy typically resolves within 2 to 4 months after cessation or lowering of the dosage of cyclosporine with or without the use of systemic prednisolone. In one report 69% of patients had complete resolution of the retinal findings and 46% of patients fully recovered their baseline visual acuity. Because of the relatively favorable prognosis and non progressive nature of BMT retinopathy aggressive treatment is not necessary.

Infection

Infections in the post bone marrow transplant period is a major cause for mortality in recipient patients.[38] However ocular infections are relatively uncommon after haematopoietic stem cell transplantation. Ocular infections usually affects the posterior segment and the incidence is around 2 %. [30]

Viral infections :

CMV retinitis is seen in about 1% of patients after BMT .[39] In solid organ transplantation the incidence is 2 to 15 %[40,41,42,43] Repeated treatment with antithymocyte globulin may lead to immune dysfunction that could increase the likelihood of CMV retinitis. Certain immunosuppressive agents such as mycophenolate mofetil has been associated with increased risk of systemic CMV infections in BMT. Visual outcome from CMV retinitis can be devastating.[44] ln most cases total blindness occurs, and is seen in three out of five patients treated adequately with antiviral regimen. CMV retinitis is more in HLA matched unrelated donor transplants than in HLA matched related sibling transplants. It responds well to antiviral agents. The prophylactic use of Valacyclovir for CMV infection in BMT has been proposed. Treatment is with Foscarnet and intraocular injection of Gancyclovir.[45]

Another cause of viral retinitis is ***Herpes zoster***.[46] Clinical features of herpes zoster retinitis are similar to those for acute retinal necrosis. The infection typically responds well to intravenous Acyclovir therapy.

Fungal infections:

Fungal infection is not an uncommon posterior segment complication. In one study fungal retinitis and endopthalmitis were the most common intraocular infections after bone marrow transplantation. Among them Candida and Aspergillosis are common.[30]

Fungal infections occur early after bone marrow transplantation with a median time of fifty seven days. In solid organ transplants Aspergillus retinitis is more common.[47,48] The primary focus of Aspergillus is subretinal or subretinal pigment epithelium. Vitreous biopsy may not yield positive results in Aspergillosis. Disseminated Fusarium infection with secondary fungal endophthalmitis can occur.[49]

Toxoplasmic retinochoroiditis [50]

This is a reactivation of the existing ocular toxoplasmosis. Infection may also represent primary ocular disease. Toxoplasmic retinochoroiditis typically occur within three to six months and can be either unilateral or bilateral. With appropriate antibiotic therapy it can usually be controlled.

Hematological complications

In the early post transplant period hematological abnormalities including anemia, hyperviscosity syndromes and thrombocytopenia are common due to the bone marrow aplasia and chemotherapy [51,52] These changes predispose to vitreous hemorrhage, intraretinal hemorrhages and other hemorrhagic complications.[53,54] Thrombocytopenia is

the most important factor in the development of hemorrhage. The incidence is about 3.5%. The majority of hemorrhagic complications are observed six months after BMT with the median time of 51 days.[38]

Other complications :

Central serous choreoretinopathy (CSCR) is more common after solid organ transplantation.[31] Pathogenesis of CSR is believed to be associated with combined effects of high dose corticosteroids, emotional stress, systemic hypertension and cyclosporine. There may be also retinal pigment epithelial changes caused by choriocapillaries ischemia leading to serous retinal detachment. Visual prognosis is generally good and the treatment of photocoagulation may be needed only in refractory cases.

Bilateral optic disc edema may occur in 2.8%[30] Optic disc oedema is due to cyclosporine related toxic effects or increased pressure or both. Cyclosporine induced retinal toxic blindness after BMT can occur.[55]

Ocular manifestations of graft versus host disease

Because of other life threatening systemic complications in patients with GVHD, ocular manifestations may often be overlooked. This at least partially explains the sparse documentation in literature of ocular complications in this disease. Ocular features occur in approximately 60 to 80% of patients with GVHD.[56] Ocular problems are

uncommon in acute GVHD, however ocular manifestations like keratoconjunctivitis sicca, sterile conjunctivitis, cicatricial lagophthalmos, cataracts and retinal micro vascular occlusive disease can occur due to chronic GVHD.

Dry eye associated with chronic GVHD is the most frequent ocular complication after SCT (40 - 60%) followed by meibomian gland dysfunction (48%) and retinal hemorrhage (35 to 40%).[23] GVHD can involve any part of the eye

Lids[57]

1. Dermatitis, acute and chronic
2. Lagophthalomos and ectropion from chronic lid inflammation
3. Loss of cilia

Lacrimal apparatus: Decreased aqueous secretions

Conjunctiva

1. Conjunctivitis
2. Xerosis secondary to decreased tears

Cornea

1. Superficial punctate keratitis
2. Persistent epithelial defect
3. Ulceration – infectious / sterile

Uvea

1. Iritis
2. Iridocyclitis
3. Choroiditis

Posterior Segment Complications

1. Microvascular retinopathy,
2. Intraretinal hemorrhage
3. Vitreous hemorrhage

Lids

Lids may be involved as part of the acute or chronic systemic skin changes associated with GVHD. Chronic lid inflammation may lead to lagophthalmos and ectropion. Loss of cilia is common with generalized skin involvement.

Keratoconjunctivitis sicca

Dry eye as a result of lacrimal gland dysfunction is one of the commonest manifestation of chronic GVHD. Even in patients with acute GVHD without ocular complications there is an increased risk for developing dry eye in the later stages.[58] In most cases, the severity of the systemic chronic GVHD correlates with the severity of the dry eye.

Incidence

Dry eye after SCT has an incidence of 40 - 60%.[23] In a multicentric retrospective cohort study dry eye syndrome developed in 19% of patients between 3 and 127 months after BMT. In this study 69% with dry eye syndrome had systemic GVHD, compared with 30% without dry eye.[59]

Approximately half the patients who undergo SCT develop dry eye 6 months later.[26] Severe dry eye resembling Sjogren's syndrome progress rapidly after the onset of symptoms in the majority of these patients. The median time from transplantation to diagnosis of dry eye was 171 ± 5.9 days.[26]

Pathology

Lacrimal gland specimens from patients with dry eye show prominent fibrosis, increase in CD4 stromal fibroblasts in the glandular interstitium and infiltration of T cells in to the periductal areas.[60] Periductal fibroblasts are involved in the fibrogenic and immune processes by interacting with T cells in the lacrimal gland of patients with chronic GVHD resulting in rapidly progressive dry eye.

Activated fibroblasts synthesize an excess amount of extracellular matrix resulting in rapid interstitial fibrosis. On the other hand CD8 lymphocytes which are activated through antigen recognition and the helper function aided by CD4 cells infiltrate and destroy the duct epithelium. Multilayered basal lamina of ducts, lobules and vessels is seen. This is the result of repeated damage and repair due to the immune process. The degree of thickening correlates with the severity of dry eye.

Risk factors

GVHD is the major risk factor for the development of dry eye.[9] KCS occurred more frequently in patients with chronic GVHD than in those with acute GVHD. Dry

eye is observed in patients receiving autologous or syngenic transplants who are not at risk for GVHD implying a cause beyond a simple alloreactive immune reaction.[61]

As conditioning regimens, TBI administered as a single dose rather than in fractions and chemotherapy alone before BMT, both increase the risk of keratoconjunctivitis sicca.[61]

Clinical Features

Dry eye after BMT is clinically similar to Sjogren's syndrome in that both are characterized by decreased lacrimation. Patients with GVHD have a compromised epithelium as a result of lacrimal gland hyposecretion. They may also have a lower threshold for cytotoxicity from radiation or chemotherapy. Usually patients are asymptomatic. Punctate keratitis, persistent epithelial defects, corneal keratinisation, ulceration and perforation may be seen as a sequelae of dry eye.[9]

Diagnosis

The diagnostic tests for dry eye[62-65] is given in the Appendix.

Prognosis

In most patients KCS persists after remission of GVHD. In one study none of the patients had normal tear function in four years of follow up.[4] In another study resolution of tear function occurred in 8% of affected GVHD patients.[66]

Conjunctival GVHD

In a prospective study of 162 patients who had undergone allogenic BMT, Jack and co workers reported findings that implicated the conjunctiva and the cornea as immunologic targets in GVHD. Histological examination revealed changes similar to those seen in cutaneous GVHD, including lymphocytic migration into the basal epithelium of the conjunctiva, presence of dyskeratotic cells and even subepithelial microvesicle formation and total separation of the epithelium in more severe cases.[5]

The median onset after transplantation was about 14 days after their first manifestation of acute GVHD.[58] The degree and severity of the conjunctival disease tends to correspond with the severity of the systemic disease.

Jabs and coworkers proposed a system for the clinical staging of conjunctival and ocular surface GVHD[5]

Stage I : Characterized by conjunctival hyperemia

Stage II : Conjunctival hyperemia with the additional findings of a chemotic response or serosanginous exudates

Stage III : Pseudomembranous conjunctivitis

Stage IV : Pseudomembranous conjunctivitis with epithelial sloughing

Within days of appearance of acute GVHD, hemorrhagic conjunctivitis similar to that of viral hemorrhagic conjunctivitis may be noted. This finding often occurs in patients who are morbidly ill from acute GVHD. Hemorrhagic conjunctivitis is followed by the development of purulent conjunctivitis within three to four days. Though numerous polymorphonuclear leucocytes are present bacterial, fungal and viral cultures are generally sterile. During this exudative phase, upper tarsal ulceration can be

observed. There is scarring of the conjunctiva following resolution of the inflammatory changes. In some cases, conjunctival scarring may be found in patients without exudative or ulcerative conjunctivitis. Furthermore massive filamentary keratitis and sloughing of the corneal epithelium similar to those seen in massive recurrent corneal erosion can occur in patients with acute GVHD.

Tanin and associates showed that the conjunctival epithelium in patients stricken with GVHD reflects characteristic features of acute GVHD with infiltration of mononuclear cells expressing mature killer cells markers, suggesting that the pseudomembranous conjunctivitis associated with GVHD is the result of very acute cytotoxic form of GVHD.[67]

Although pseudomembranous conjunctivitis is uncommon in GVHD, its presence has been considered a marker for systemic involvement and is associated with a poor prognosis.[67]

Treatment of dry eye

Medical Management

Preservative free artificial tears[68]

Methylcellulose eye drops[69]

Autologous serum drops[70]

Epidermal growth Factor[71]

Fibronectin[72]

Retinoic Acid[73]

Topical Steroids[74]

Tacrolimus[74]

Cyclosporine A[75] can be used

Systemic immunosuppressants such as cyclosporine (CsA) can be effective for treating ocular GVHD including lacrimal gland dysfunction. However, systemic immunosuppression is not generally prescribed for patients whose sole manifestation of GVHD is ocular complications as it may negate the overall graft-vs-tumor effect and decrease the patient survival. Topical Cyclosporine A is an immunomodulator. The anti-inflammatory effect arises largely from its ability to prevent the activation of T cells and the resulting production of cytokines and other inflammatory agents. It is found to be useful in patients with severe dry eye.[75] Some studies say that penetration of topical agents is not effective, therefore sustained release subconjunctival CsA implant has been developed to bypass these epithelial barriers and significantly increase the CsA concentrations in the lacrimal gland to treat aqueous tear deficiency related to GVHD. A study on efficacy of cyclosporine implant in these patients is currently underway at Betesda in the USA.[76]

Treatment of **filamentary keratitis** requires treatment of the underlying dry eye condition. Patients with severe symptoms frequently benefit form mucolytic agents (N - actylcysteine).

The management of persistent epithelial defects requires in addition to maximizing dry eye therapy, application of a bandage contact lens with judicious use of topical steroids with appropriate antibiotics to protect the compromised epithelium. Surgical intervention becomes necessary in selected cases of non healing epithelium or stromal disease which does not respond adequately to the recommended regimen.

Surgical management

If the ocular surface involvement is severe or progressive , **punctual occlusions** should be considered. There is a low threshold for the use of **plugs** in these patients as the plugs often dislodge early because of frequent rubbing of the eyes. **Heat cautery** or **laser punctal stenosis** may be used as an alternative to achieve the desired degree of tear preservation and surface hydration. [77]

Tarsorrhaphy is a safe and time tested approach in these patients. Evidence of corneal melting is an ominous sign that may require the use of **tissue glue**. Multilayered **amniotic membrane transplantation** has been used to manage corneal perforation resulting form chronic GVHD.

Cataract

In additional to the ocular findings associated with compromised epithelium, **c**ataract formation is common and can occur in 83% patients with long term follow up[78] Higher incidence is seen in those with GVHD probably due to use of long term

corticosteroids. The incidence of cataract is also high in patients who had undergone TBI and had used potentially cataractogenic chemotherapeutic agents such as Busulphan.[79]

Multivariate analysis showed that the total dose and the duration of corticosteroid therapy were the most important risk factor. In another study the incidence of cataract was 2.3% at 2 years, but it did not cause significant visual impairment.[80] The cataract was posterior subcapsular and surgery can be safely performed in GVHD patients.[9] Phacoemulsification with IOL is done with adequate preparation of the ocular surface including lubricants, punctal occlusion and topical anti inflammatory drugs.

Recurrent bilateral multifocal **chorioretinitis with pan uveitis** has also been noted. Rarely patients may also present with uveitis which is thought to be a result of direct immunogenic attack of donor lymphocytes against host histocompatability antigens. One rare case of scleritis with choroidal detachment as the initial clinical manifestation of acute GVHD on day 40 has been reported.[26]

Posterior segment complications:

A variety of complications can occur and they include microvascular retinopathy, intraretinal and vitreous hemorrhage and infections.

CSR is an uncommon complication.

MATERIALS AND METHODS

Study design:

Descriptive, observational study

Study population*:*

Patients with aplastic anemia and various hematological malignancies that required SCT

Inclusion criteria**:**

Patients who had undergone bone marrow or peripheral blood stem cell transplant .

Data collection:

The principal investigator evaluated the patients for any ophthalmological complications The information was entered in the proforma.

Methodology:

The patients who had undergone SCT had a complete ophthalmological examination.

Vision: Best Corrected visual acuity using Snellens chart and refraction.

Lids : Examined for

Acute dermatitis /erythema with rash / generalized

erythroderma with blisters / desquamation

Chronic dermatitis diagnosed if there is ectropion /

lagophthalmos / scarring

In the available literature, there is controversy regarding the criteria for diagnosis of dry eyes based on clinical diagnostic tests. There is no gold standard for the diagnosis of dry eye. A number of diagnostic tests have been described in the literature for evaluation of dry eyes. All clinical tests have limited diagnostic value if performed

individually or in the absence of severe symptoms. It is not uncommon to find an abnormality of a single tear function test. Thus for diagnosis of dry eyes more than one test should be abnormal.

Dry eye:

The tests done for the detection of dry eye were

Schirmer's test with paracaine 0.5% < 6mm at 5 minutes,

Debris in tear lake TBUT < 10 seconds and presence of thinning / pannus / filaments / ulcers .

Definitions of the area and density grades of superficial punctate keratopathy on fluorescein staining

Area (total sum of the affected area)

A0: no punctate staining

A1: area occupies less than one third of the cornea

A2: area occupies one third to two thirds of the cornea

A3: area occupies more than two thirds of the cornea

Density

D0: no punctate staining

D1: sparse density

D2: moderate density

D3: high density and lesions overlap

Criteria for diagnosis of dry eye (At least **2/4** of the following criteria present)

1. Tear lake < 0.2mm / Tear debris
2. Tear Break Up Time < 10 seconds
3. Superficial punctate keratitis
4. Schirmer's test 1b

Upper tarsal Conjunctiva:

Examined for signs of GVHD – Hyperemia / chemosis / pseudomembrane / epithelial loss and scarring.

Uveitis : Diagnosed by presence of cells and flare in anterior chamber and / or vitreous

Pupils: Pupillary reflexes and presence of relative afferent pupillary defect

IOP: Measured by Goldmann's applanation tonometer

Cataracts: Diagnosed by slit lamp examinations after dilatation with 1% tropicamide

Grading

Classified according to the Japanese Co operative Cataract Epidemiology Study Group System[85]

Nuclear colour

I Pale yellow

II Yellow

III Yellowish brown

IV Brown/ black

Posterior subcapsular cataract

I Opacity < normal pupil

II < moderate size pupil

III opacity > moderate sized pupil

Dilated fundus : Examination with a 20D and 90D at slit lamp

Disc: Examined for Glaucoma

CDR>0 .7, Neuroretinal rim and

Nerve fibre layer defect, oedema, margins and SVP

BMT Retinopathy: Cotton wool spots, telangiectasia, microaneurysm, macular edema, hard exudates, hemorrhages.

Infections: CMV retinits, herpes zoster retinitis, fungus retinitis, Toxoplasmosis and endopthalmitis.

Hematological complications: Vitreous hemorrhage and intraretinal hemorrhage.

All patient included in this study would have undergone BMT according to the standard protocols used in Christian Medical College & Hospital, Vellore. The preparative marrow ablative regimens were standardized according to the pre transplantation diagnosis

In general the pre BMT conditioning for

Acute Myeloid Leukaemia (AML) and Chronic Myelod Leukaemia (CML)

- Intravenous IV Busulphan 16mg per kg total dose over 4 days plus
- IV Cyclophosphamide 120mg per kg over 2 days .

Acute Lymphoid Leukaemia(ALL)

- IV Cyclophosphamide 120mg per kg over 2 days plus

- Total body irradiation 12 Gray over 3 days (2 Gray twice a day with linear accelerator)

Aplastic anemia

. IV Fludarabine 180mg per msq over 6 days plus
- IV Cyclophosphamide 120mg per kg over 2 days +/-
- Antithymocyte globulin 10mg per kg per day for 4 days.

Thalassemia

- IV Busulphan 16mg per kg total dose over 4 days plus
- IV Cyclophosphamide 120mg per kg over 4 days and
- Antithymocyte globulin 10mg per kg per day for 4 days

TBI is given in acute lymphocytic leukemia and if there is CNS involvement.

GVHD prophylaxis

Cyclosporine IV 5mg per kg per day in divided doses for 3 to 6 months in leukemia and for one year in thalassemia and aplastic anemia plus

Methotrexate 10mg per metre sq per day on day 1 and 7mg per metre sq per day on days 3 , 6 and 11.

IV Methylprednisolone 1mg per kg per day tapered over one month if the patient had jaundice.

GVHD staging

Skin GVHD graded according to the extent of involvement of the total body surface area. Clinical staging of liver disease is based on the elevation of the liver enzyme and the bilirubin levels while staging of the gastrointestinal involvement is based on the volume of diarrhea.

Data Analysis : Data entry was done using SPSS version. Statistical analysis was done using a Statistical Package STATA.

Statistical Methods

Statistical Methods employed in the study was the Chi Square Test to test the association between

Dry eye and GVHD

Systemic infections and ocular morbidity

Dry eye in bone marrow compared to peripheral blood stem cell transplant

Conjunctival GVHD in bone marrow compared to peripheral blood stem cell transplant.

Results

A total of 40 patients who had undergone bone marrow and peripheral blood stem cell transplantation were studied. The majority were males. The mean age was 24.3 years (SD 12.4). The age range was from 5 to 51 years.

Age wise grouping of patients who underwent transplantation is shown in the following table

Table showing age wise distribution of patients :Table 1

Age group	Number of patients	%
< 10 years	7	17.5%
11 - 20 years	7	17.5%
21 - 30 years	12	30%
31 - 40 years	10	25%
41 - 50 years	3	7.5%
> 51 years	1	2.5%

In our study the majority of patients who underwent transplantation were below 30 years of age.

Transplant details

Indications *:*

Leukemias were the commonest indications for transplantation (table 2) The other indications were aplastic anaemia, thalassemia and myelodysplastic syndromes.

Table showing distribution of indications for bone marrow transplantation: Table 2

Indication for BMT	Number of

	patients	%
Leukemia	21	52.5%
Aplastic anemia	6	15%
Thalassemia	6	15%
Myelo dysplastic syndrome	2	5%
Others *	5	12.5%

- *Others:,* Paroxysmal Nocturnal Haemoglobinuria, High grade peripheral T cell lymphoma, Blackfan Diamond syndrome, Granulocytic sarcoma, Dyskeratosis congenita.

Types of bone marrow transplantation:

39/40 (97.5%) of the patients studied had allogenic transplantation. Only 1/40 (2.5%) had autologous transplantation. Majority 25/40 (62.5%) had Allogenic / PBSC/HLA matched transplantation.

Table showing distribution of types of transplants :Table 3

Type of transplantation	Number of patients	%
Allogenic / PBSC/HLA Matched	25	62.5%
Allogenic / BMT/HLA Matched	13	32.5%
Autologous /PBSC/ HLA Matched	1	2.5%
Allogenic cord blood HLA Matched	1	2.5%

Conditioning:

For conditioning prior to BMT 31/40 (77.5%) received chemotherapy and the remaining 9 (22.5%) received both, total body irradiation and chemotherapy. These were based on standard protocols for each disease.

Table showing distribution of conditioning regimen: Table 4

Conditioning	**No of patients**	**%**
Chemotherapy alone	31	77%
Chemotherapy & Total body irradiation	9	23%.

Engraftment

The mean engraftment time was 19 days (SD 10.5). The range was from 10 days to 69 days.

Table showing distribution of engraftment time: Table 5

Engraftment time	Number of patients	%
< 10 days	1	2.5%
10 to 20 days	26	65%
21 to 30 days	10	25%
31 to 40 days	1	2.5%
> 40 days	2	5%

Infections

50 % of the patients studied had systemic infection post BMT. Bacterial sepsis was the commonest, seen in 11/40 (27.5%) patients. 8 /40 (20)% of patients had multiple sites of infection. The remaining patients did not have any infection. None of the patients had ocular infection.

Systemic graft vs host disease

24/40 patients (60%) of patients had developed systemic graft versus host disease (GVHD). 18/40 (45%) had acute GVHD and 6/40 (15%) had chronic GVHD.

Table showing distribution of sites involved in graft versus host disease (acute and chronic): Table 6

Sites of GVHD	Number of patients	%

Skin	14	58%
Liver	12	50%
GIT	8	33%

Skin was the commonest site involved in GVHD seen in 58% of the patients, followed by liver and then the gastrointestinal tract.

Table showing distribution of multiple sites involvement in graft versus host disease:

Table 7

GVHD involving multiple sites	Number of patients	%
Skin and liver	5	12.5%
Skin and GIT	2	5 %
Liver and GIT	3	7.5%

14 (35%) patients had GVHD involving only a single site while 10 (25%) had GVHD involving multiple organs (ie) skin, liver and GIT

Ocular Morbidity in the post transplant period

26/40 (65%) patients had ocular morbidity following transplantation. 18/40 (45%) of the patients had more than one type of complication in the eye.

Dry eye was the commonest ocular morbidity seen after transplantation seen in 57.5% patients. This was followed by **Conjunctival GVHD** in 35% of patients and 15% had **cataract.** The cataracts were mostly grade one posterior subcapsular cataract. Of the remaining 34 patients 2 patients were pseudophakic prior to the transplant. Pre- existing vitreous hemorrhage and refractive error was seen in 7.5% each. 5% of patients had **retinal complications** like cystoid macular oedema and epiretinal membrane.

Table showing distribution of patients with ocular morbidity: Table No: 8

	Number of patients	*%*
Dry eye	23	57.5%
Conjunctival GVHD	14	35%
Cataracts	6	15%
Vitreous Hemorrhage	3	7.5%
Refractive error	3	7.5%
Retinal changes	2	5%
Lid changes	1	2.5%

* Retinal changes – ERM (epiretinal membrane), CME (cystoid macular edema)

16/23 (69%) of the patients with dry eye had received chemotherapy as conditioning therapy while 7/23 (31%) patients had received both chemotherapy and radiation therapy.

Only one patient had **lid changes** causing an ectropion. None of the patients studied had uveitis, pupillary abnormalities, raised intraocular pressures or ocular infections.

Multiple ocular complications

Few patients had multiple ocular complications as shown in Table 9. The most common was dry eye associated with conjunctival GVHD seen in 32.5% of patients. This was followed by dry eye with cataract seen in 7.5% of patients. One patient with vitreous hemorrhage had an associated dry eye and one patient had conjunctival GVHD with a pre existing vitreous hemorrhage.

Table showing distribution of multiple Ocular Complications Table No :9

Multiple Ocular Complications	No of patients	%
Dry eye + conj GVHD	13	32.5%
Dry eye + Cataract	3	7.5%
Dry eye + Vitreous Hemorrhage	1	2.5%
Conj GVHD + Vitreous Hemorrhage	1	2.5%

Visual Acuity

Visual impairment. ie Best Corrected Visual Acuity (BCVA) <6/6 was seen in 37.5%. Severe dry eye was the commonest cause seen in 20%. These patients had BCVA varying from 6/36 to 6/6p. Pre-existing refractive error and vitreous hemorrhage causing decrease in vision was noted in 7.5% each. Two patients had retinal changes after the transplantation.

Table showing distribution of causes of visual impairment Table No: 10

Causes of visual impairment	Total number	%
Dry eye	8	20%
Refractive error	3	7.5%
Retinal change	2	5%
Vitreous hemorrhage	3	7.5%

Dry eye was the commonest ocular complication seen after transplantation. Dry was also the commonest cause for visual impairment.

Table showing distribution of criteria for dry eye Table No :11

Dry eye criteria	Total 23 patients	
Tear film Break Up Time<10 secs	23	100%
Tear lake<0.2mm\Tear Debris	20	87%
Superficial Punctate Keratitis	15	65%
Schirmer test I b	13	56.5%
Filamentary keratopathy	3	13%

Pannus	1	4.3%

All the patients with dry eye had an altered tear break up time. A decreased tear lake with or without associated tear debris was the next most common finding in dry eye followed by superficial punctate keratitis. Three patients had severe dry eye with filamentary keratopathy. None of the patients studied had corneal thinning.

All the patients with dry eye had a positive tear break up time less than 10 seconds. Of these patients more than 18/23 (78%) had at least three criteria positive for the diagnosis and 12/23 (52%)had four criteria positive for dry eye.

Conjunctival GVHD

Conjunctival GVHD was seen in 35% (14/40) of patients. Hyperemia was the commonest manifestation. Chemosis was not noted in any patient.

Table showing distribution of manifestations of conjunctival GVHD

Table No: 12

Conjunctival GVHD Manifestations		
Hyperemia	8	20%
Scarring	5	12.5%
Epithelial loss and Pseudomembrane	1	2.5%

Of the 14 patients who had conjunctival GVHD, 10 (75%) of them had an associated systemic GVHD.

Table showing distribution of interventions: Table No 13

Intervention	**Patients**	**%**
Lubricants	17	42.5%
Lubricants + steroids	3	7.5%
Lubricants +Punctal occlusions	2	5%
Lubricants + cyclosporine	1	2.5%
Vitrectomy	1	2.5%

Most of the interventions were related to the treatment of dry eye. All the patients with dry eye were given lubricants. Three patients were given topical steroids in addition and two required punctal occlusion. One patient was started on Cyclosporine drops. One patient required a vitrectomy for a preexisting vitreous hemorrhage.

Associations:

The following associations were found on analysis:

1. Increased occurrence of dry eye in patients who had developed systemic GVHD (p Value = 0.03)
2. Increased ocular morbidity in patients with post transplant infections (p value = 0.002).
3. Same risk of developing dry with BMT and PBSCT (p value = 0.45)
4. Same risk of developing conjunctival GVHD with BMT and PBSCT (p Value 0.57)

Table showing association between systemic GVHD and dry eye - Table no: 14

		Dry eye +	Dry eye -	
GVHD	+	17	7	24
	-	6	10	16
		23	17	40

Chi square value = 4.36

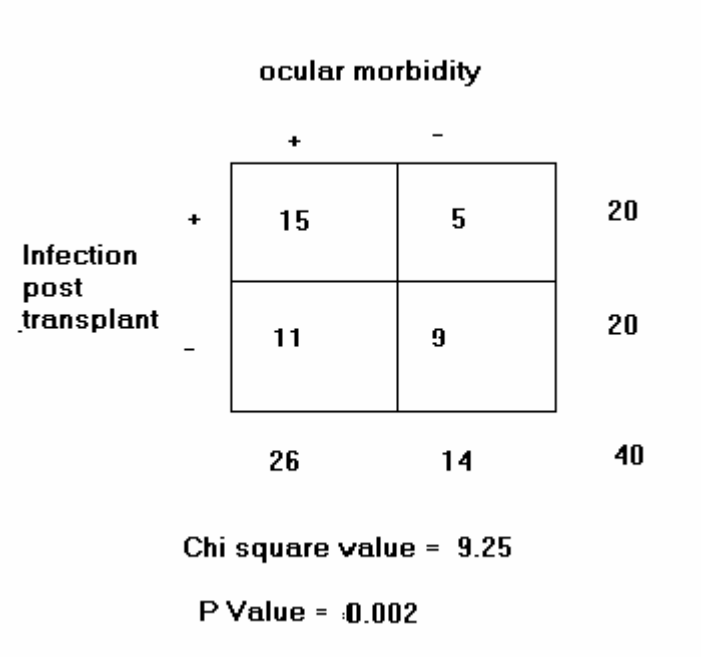
P Value =0.03

74% (17/23) of the patients who had dry eye had GVHD. And 70% (17/24) of the patients who had GVHD had dry eye. This association was found to be significant (P Value = 0.03)

Association between ocular morbidity and Systemic infections

Table showing association between ocular morbidity and systemic infections

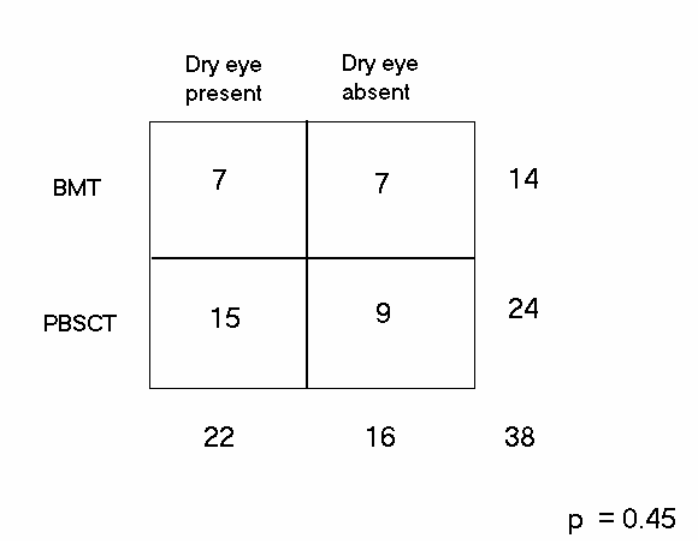
2Table no: 15



Of the 26 patients who had ocular morbidity,15 patients (57%) had infection in the post transplant period. Of the 20 patients who had infection in the post transplant period 15 (75%) had developed some ocular morbidity . This associataion was significant p value = 0.002 .

Association between dry eye in BMTvs PBSCT

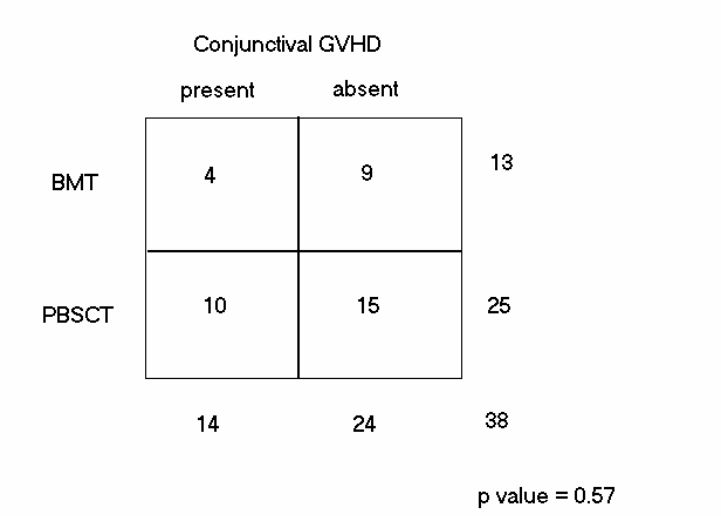
Table showing association between dry eye in BMTvs PBSCT - Table 16



Dry eye was seen in 7/14 (50%) of the patients who had undergone bone marrow transplantation. In those who had PBSCT dry was seen in 15/24 (62.5%). The difference between these two groups was not significant P value = 0.45

Association between conjunctival GVHD in BMTvs PBSCT
Table showing association between conjunctival GVHD in BMTvs PBSCT

Table 17



Conjunctival GVHD was seen in 4/13 (30.7%) patients who had undergone bone marrow transplantaion while this was seen in 10/25 (40%) patients who had undergone PBSCT . The difference between these two groups was not significant, p Value 0.57

DISCUSSION

Bone marrow and peripheral blood stem cell transplantation is a life saving procedure for an increasing number of patients. With the advent of immunology, histocompatibility testing, immunosuppressive therapy and good supportive care the pool of suitable donor marrow expands from autologous grafts to include HLA matched related individuals and fully / partially matched unrelated individuals. This increases the chance of more patients benefiting from SCT. This will result in an increased number of long-term survivors who will need specialised monitoring and management for the various post transplant complications and morbidity.

We studied 40 patients in the post transplant period who had BMT or PBSCT done in our hospital. Ocular morbidity was seen in 65% of them. These morbidity could be broadly classified as Ocular surface diseases – **dry eye**(57.5%), **conjunctival GVHD**(35%), **cataracts**(15%) **and retinal changes(** 5%).

As **conditioning regimen** prior to transplantation 77% received chemotherapy alone and the rest 23% had both radiation and chemotherapy. Sullivan had shown a higher incidence of dry eye in patients receiving radiotherapy in addition to chemotherapy for conditioning.[84] In our study 77% of the patients who had received radiation prior to the transplant had developed dry eye while this was seen in 53% who had received only chemotherapy. But the number of patients who received chemotherapy and radiation were only nine compared to 31 who had only chemotherapy and hence an association could not be established.

In our study population 97% had **allogenic** transplants (allogenic PBSCT in 62.5% and allogenic BMT in 32.5%). Lawrence et al have shown that allogenic PBSCT has an increased incidence of systemic GVHD.[4] Ocular morbidity like dry eye and conjunctival GVHD is seen more in patients with systemic GVHD.[26] However we could not find a statistically significant difference in the incidence of either dry eye or conjunctival GVHD in patients who had allogenic PBSCT vs allogenic BMT in our study. (p values 0.45 and 0.57 respectively.)

Ocular surface disease is the most prevalent problem after haematopoietic stem cell transplantation. Of the 65% (26/40) of patients with ocular morbidity, the majority of them ie 57% (23/40) were noted to have findings suggestive of dry eye. Jack and Hicks have noted dry eye syndrome in 40 out of 90 patients. However they have not mentioned how many of their patients had developed GVHD.[82] In another study by Kenyon et al the incidence of dry eye was as high as 60% in patients with GVHD.[68] This developed three months after BMT and included dry eye with corneal sequelae causing punctate keratitis, persistent epithelial defect, and sterile /infectious stromal ulceration. This illustrates the fact that dry eye is more often seen in patients with chronic GVHD and that the severity of dry eye is also more when the patient has GVHD.

The age of the patients ranged from 5 to 51 years. Of the seven patients less than 10 years of age, only one of them had dry eye. This is in keeping with a study which proved that the prevalence of dry eye syndrome is less in **children** than in adults owing to

healthier and faster regeneration of epithelial cells.[3] However the number of children in our study was too small to establish a statistical significance.

None of the patients developed persistent epithelial defect, sterile or infectious stromal ulceration. Most of the patients as in other studies responded to topical ocular lubricants. Out of 40, three required topical steroids and two required punctal occlusion. Only one patient was given topical cyclosporine. The long term efficacy of cyclosporine drops in treatment of dry eye in GVHD has to be evaluated on follow up.

None of the patients required a major surgical intervention like Tarrsoraphy, conjunctival homograft, amniotic membrane transplantation or penetrating keratoplasty.

In this study there was a **significant association** between development of **dry eye and presence of GVHD** (p value 0.03). This finding has been reported in other studies.[4] Our study also showed a **significant association** between **ocular morbidity and systemic infections** in the immediate post transplant period. However the exact reason for this could not be ascertained. Literature search did not reveal an increased incidence of ocular morbidity in the presence of systemic infections in other studies.

Conjunctival GVHD

Conjunctival GVHD is a marker for severe systemic GVHD and development of higher stage of ocular GVHD was found to be significantly associated with more severe

forms of both acute and chronic systemic GVHD.[7] In this study of the 14 patients who had conjunctival GVHD, 10 (75%)of them had an associated systemic GVHD.

Jabs et al have reported the incidence of conjunctival GVHD to be 12% in acute GVHD and 11.1% in chronic GVHD.[19] In the above study, most patients presented with pseudomembrane **- grade 3 conjunctival GVHD.** This is in contrast to our study where conjunctival GVHD was seen in 35% patients and the commonest finding was hyperemia of the conjunctiva - **grade 1 conjunctival GVHD**. Only one patient had a pseudomembrane formation which is a higher grade of conjunctival GVHD.

.

Cataract

Cataract formation is common in allogenic stem cell transplant patients[52,78,79] occurring in as many as 83% with long term follow up.[78] There is an association between cataract and GVHD which is said to be due to the use of long term **corticosteroids.** In addition pre transplant **TBI** conditioning is also associated with higher incidence of cataract.

Cataract was noted in 15% of our patients and all of them had grade 1 **posterior subcapsular** cataract. As we had not seen the patients prior to transplantation we could not attribute the cataract to transplantation. Two patients were pseudophakic prior to the transplant..

Cataract surgery with intraocular lens implantation can be safely performed in GVHD patients.[9] Preoperative ocular surface rehabilitation, including lubricants, punctal

occlusion and topical anti-inflammatory agents is essential to reduce the incidence of complications after the surgery.

Posterior segment complications

Incidence of posterior segment complications post haematopoietic stem cell transplantation has been reported to be around 12%.[30] These complications although rare, can have significant visual consequences and implications. In our study only 2 of the patients (5%) developed posterior segment complications. One had **cystoid macular edema** and the other had **epiretinal membrane**. Cystoid macular oedema has not been described in the literature in post transplant recipients. None of the patients developed BMT retinopathy/ retinal infections or optic disc oedema.

Three patients had pre existing vitreous hemorrhage prior to SCT. This could be secondary to the disease or thrombocytopenia occurring after chemotherapy.

Miscellaneous Findings

The cutaneous manifestations of GVHD can affect the eyelids. Dermatitis, lagophthalmos, ectropion, poliosis, madarosis, vitiligo can occur. Only one of our patients developed an **ectropion.** This was secondary to the skin GVHD that the patient had.

The first and major limitation of our study was that it involved only a subset of patients who were well enough or were willing to come for an ophthalmic evaluation and hence did not include all the patients who had come for a review post transplant. Therefore the profile of ocular morbidity described may not be accurate.

We do not know the pre BMT status of the patient. This is important because the conditions requiring transplantation such as leukaemias and anaemias by themselves are associated with significant ocular morbidity due to the associated anaemia, thrombocytopenia and polycythaemia.

The acute ocular complications could not be ascertained because the patients were not evaluated in the immediate post transplant period. This was due to the fact that they were under barrier nursing or they were acutely ill to undergo a thorough ophthalmologic evaluation.

CONCLUSION

- 65% of the patients post bone marrow and peripheral blood stem cell transplantation had ocular morbidity.
- Dry eye (57.5%) was the commonest finding followed by conjunctival GVHD (35%) and posterior subcapsular cataract(15%).
- Increased incidence of ocular morbidity is seen in patients with post transplant infections .
- Increased occurrence of dry eye is seen in patients who had developed systemic GVHD
- The risk of developing dry eye is the same in patients who have had BMT and in those who had PBSCT
- The risk of developing conjunctival GVHD is the same in patients who have had BMT and in those who had PBSCT

Regular ophthalmic examination is therefore essential especially for patients who have had systemic infections and or systemic graft versus host disease for early detection and treatment of the potential complications.

REFERENCES

1 Bach, Albertini, J Anderson Bone Marrow Transplantation in a patient with Wiscott Aldrich Syndrome Lancet19682 1364-1366

2 Joan SK, Dennis S C Lam,Chi K Li : Ocular complications of Pediatric Bone marrow transplantation Opthalmology Vol 106 No 1 Jan 1999 : 160 – 164

3 Donney W Suh, Mark S Ruttum, Bradley J S Ocular findings after bone marrow transplantation in a Pediatric population-Ophthalmology Vol 106 No8 Aug 1999 : 1564 – 1570.

4 Lawrence, Hirst, Tutska The eye in bone marrow transplantation I Arch Ophthal Vol 101 April 1983 580-584

5 Douglass A.Jabs, John Wingad, Richard Green : The eye in bone marrow transplantation III conjunctival graft –vs Host disease – Arch of ophthalmology vol 107 Spt 1989 .1343 – 1348

6 Geller,Devine, Toole. Allogenic bone marrow transplantation with matched unrelated donors for patients with haematological malignancies using preparative regimen of high dose cycloposphamide and total body irradiation. Bone Marrow Transplant 1997 Aug20(3) 219-25

7 Thomas ED Storb R Clift RA Bone marrow transplantation N Eng J Med 1975;292:832-43

8 Cutler C, Antin JH: Peripheral Blood Stem Cells for Allogeneic Transplantation: A Review. Stem Cells 2001 Mar; 19(2): 108-117.

9 Nicholas G, Anderson and Carl Regillo : Ocular manifestations of Graft versus host disease : Current opinion ophthalmology 2004 15 : 503 – 507

10 Anderson D, Defort T, Burns L : a comparison of related donor peripheral blood and bone marrow transplant ; importance of late onset chronic GVHD and infections. Biol Blood Marrow transplant 2003 Jan 9 (1) 52 – 9

11 Weisdorf, Haake, Blazar Treatment of acute to moderate GVHDafter Allogenic BMT. An analysis of Clinical risf factors .Blood75:1024-1030,1990

12 Jack, Jack: Ocular Manifestations of GVHD.Arch Ophthal 101:1080-1084,1983

13 Guian EC, Griblean JG, Bouissiotie VA; Pivotal role of the CD28 pathway in transplantation tolerance and tumour immunity ; Blood 1994 84 3261 -3286

14 Brown D ; Graft versus host disease ; Current opinion Oncol 1994 6 : 358 - 364

15 Krengu W, Ferrara JL; GVHD and the Th1/ Th2 paradigm ;Immunology Res 1996 15: 50 – 73

16 Antin JH, Ferrara JL, Cytokine dysregulation and acute GVHD; Blood 80:1992 2964 -2968

17 Armitage JO ;BMT ; New England Journal of Med 330 1194 , 827 – 838

18 Brown D; Graft versus host disease ; Current opinion Oncol 1994 6 : 358 - 364

19 Jabs, Wingard , Green The eye in BMT 111 Conjunctival GVHD; Arch Ophthalmology Vol107 Sep1989

20 Siadak M, Sullivan KM, : The management of chronic graft versus host disease. Blood Rev 1994 8 :154 - 160

21 Shulman HM, Sale GE, Lerner KG; Chronic cutaneous graft versus host disease in man .American Journal of Pathology 1978 , 91 ; 545 – 70

22 Larazus HM, Rowe JM, New and experimental therapies for treating graft versus host disease ; Blood Rev 1995 ,9 117 – 133

23 Vogelsang GB, Farmer ER, Hess AD ; Thalidomide for the treatment of chronic graft versus host disease ; N Eng J Med 1992 326 ; 1055 – 1058

24 Sullivan KM, Shulman HM, Chronic graft versus host disease in 52 patients : Adverse natural course and successful treatment with combination immunosuppression . Blood 1981 ; 57 ; 267 – 276.

25 Sullivan KM, Witherspoon RP, Storb RB ; Alternating day cyclosporine and prednisolone for treatment of high risk chronic graft versus host disease.Blood 1988 , 72- 555 -561

26 Ogawa and Kuwana : Dry eye associated with chronic GVHD : Cornea Vol 22 Supplement 1 . Oct 2003 : S 21 – 27

27 Barletta, Fannous, Curtis E. Margo Corneal and Conjunctival Tovicity with low dose Cytosine Arabinoside. Am J Ohpthal May1992 Vol113 no5 587

28 Ogawa, Yakamato, Wakar . Dry eye after haematopoietic stem cell transplantation. Br J Ophthal 1999:83 1125-1130

29 Yeh PT, Hou YC, Lin WC, Wang IJ, Hu FR. Recurrent corneal perforation and acute calcareous corneal degeneration in chronic graft-versus-host disease. J Formos Med Assoc. 2006 Apr;105(4):334

30 Lowley T J, Peck G L, Moutsopoulous HM: Scleroderma , Sjogren Like syndrome and Chronic GVHD.

31 Suk J Moon and William F Mieler : Retinal complications of bone marrow and solid organ transplantions :Current opinions in Opthalmology 2003 14; 4334 –2

32 Kawase E, Azuma N, Shioda Y, Kumagai M : Infantile case of occlusive microvascular retinopathy after bone marrow transplantation**S** Jpn J Ophthalmol. 2005 Jul-Aug; 49(4):318-20.

33 A Jabs,Wingard J R; Optic disc edema after bone marrow transplantation ; possible role for cyclosporine toxicity : Opthalmology 1991 ;98 ;1294 – 1301

33 Walter SH, Bertz H, Gerling J – bilateral optic neuropathy after bone marrow transplantation and Cyclosporin A therapy. Graefes Arch Clin exp Opthalmology 2000 ;238 472 -6

34 Lopez Jimenry J, Sanchez A, Fernandez S – Cyclosporin induced Retinal toxic blindness : Bone marrow transplantation 1997 ,20 ; 242 – 245.

35 LopezPF, Steinberg P, Babbs K :BMT Retinopathy Am J Ophtalmology 1991 112;635-646

36 Bernauer W Gratwohl, A Keller A Microvascular Retinopathy in Ocular Fundus after BMT Ann Intern MED 1991 115; 925-930

37 Conskuncan NM, Jabbs D A,Dunn J.P : the sye in BMT , VI Retinal complications : Arch Opthalmology 1994 112 ;372 – 379

38 Wingard J R, Piantadosti, S Burns D : CMV Infection in BMT Recepients given cytoreductive therapy. Review of infectious disease 1990 12 793 – 804

39 Guembel HO, Ohroloff C, : opportunistic infections of the eye in immunocompromised patients .Ophthalmologica 1997 ‘ 211 :53 -61

40 Ng P,Mc Cluskey P Mc Coughan : ocular complications of heart , lung and liver transplantation - British Journal of Ophalmology 1998 82 ; 423 - 428

41 Fishburne BC, Mitrani AA, Davis J; Cytomegalovirus retinitis after cardiac transplantation : American journal of ophthalmology 1998 125 ; 104 -106

42 Aw M M,Murugasu B, Tan AW: Quantification of peripheral blood cytomegalovirus DNA for monitering recurrent CMV Retinits in Pediatric transplants recipients.Pediatric transplants 2000 ,4 ;100 -106

43 Larsson K, Lorqiust B, Rugden O, CMV Retinitis after allogenic BMT Transplantation Infect Dis 2002 4 75-99

44 Okamato T,Okada M Mori A Successful treatment of severe CMV Retinitis with Foscarnet and Intra vitreal gancyclovir in a myelosuppressed Bmt patient Bone Marrow Transplant 1997;801-803

45 Walton R C, Reed KL; Herpes zoster opthalmicus following Bone marrow transplantation in children :Bone marrow transplant 1999 23 ,1317 -1320

46 Hunt KE, Glasgow BJ, Asperigellus endopthalmitis .- an unrecognized endemic disease in orthoptic liver transplantation ophthalmology 1996 103 757 to 767

47 Cattlien AM, Loy M, Tognon S, : An unusual presentation of invasive Aspergillosis after lung transplantation. Transplant Int 2000 13 ; 183 -186

48 Robertson MJ, Socinski MA, Soiffer RJ ; Sucessful treatment of disseminated fusarium infection after autologous bone marrow transplantation for Acute Myeloid Leukemia ; Bone marrow transplant 1991 : 8 143 – 145

49 Pecock JE, Greeven CM, Crus JM; Reactivation Toxoplasmic retinochoroiditis in patients undergoing BMT : Bone marrow transplant Journal 1995 983 -87

50 Rosental AR ,; Ocular manifestations of Leukemia : Opthalmology 1983 90, 899 –905

51 Suh DW, Ruttum MS: Ocular findings after BMT in a pediatric population Opthalmology 1999 106;1564 -1570

52 Jabbs BA, Hirst LW, Greene WR : The eye in Bone marrow transplantation II Arch of Opthalmology 1983 – 101 ;585 -590

53 Bray LC, Carey PJ, Proctor SJ ;Ocular complications of BMT ;British Journal of Ophthalmology 1991 (75) – 611 614

54 Lopez Jimenry J ,Sanchez A, Fernandez S – Cyclosporin induced Retinal toxic blindness : Bone marrow transplantation 1997 ,20 ; 242 – 245.

55 Arocker – Mettinger E, Skorpik F, Grabner G ; manifestations of graft versus host disease following allogenic bone marrow transplantation . Eur J Opthalmology 1991 1 28 – 32

56 Jabs DA,Hirst LW; The eye In bone marrow transplantation II Histopathology Arch Of Opthalmology .Arch Opthalmology 1983 101 585 – 590.

57 Sale GE,Shulman HM, Schubert MM ; Oral and opthalmological pathology of Graft versus host disease in man : Predictive value of the lip biopsy, Human Pathology 1981.12 ; 1022 – 1030.

58 Tichelli A, Duell T, Weiss M; late onset Keratoconjunctivitis sicca syndrome after bone marrow transplantation: Incidence and risk factors European group

on blood and marrow transplantation (EBMT) Bone marrow transplant 1996 17 1105 – 1111

60 Ogawa, Kazuto Yamazaki, Masataka Kuwana. ASignificant Role Of Stromal Fibroblasts in Rapidly Progressive Dry Eye in patients with chronic Gvhd IOVS Jan 2001 Vol 42 no 1 111- 119

61 Tichelli, Duell, Weiss Late onset Keratoconjunctivitis Sicca after Bone marrow Transplantation Incidence and risf Factors(EBMT) Bone Marrow Transplant 17:1105-1111,1996

62 Thomas E Clinch, DominicBendetto, Norman T Felberg; Schirmers test-Arch ophthalVol101 Sept1983 1383-1386

63 Mahipal Sachdev,Santhosh Honavar,Meenakshi Thakar.Diagnostic tests for corneal diseases. IJO Vol42 no 2 89-99

64 Feenestra PG Tseng SCG Comparison of Fluoresceein and rose Bengal staining Ophthalmlology 1992;99;605-617

65 Arun Sangal. Diagnosis of dry eye-Ophthalmology today Volvi No 2 May June 2005

66 Jack MK Ocular Manifestations ofGVHD Arch Ophthalmology 1983 90 4-13

67 Janin, Favan, Castier Pseudomembraneous Conjunctivitis following BMT: Immunopathological and ultrastructural study . Hum Path 27:307-309 1996

68 Franklin, Kenyon, Tushka Ocular Manifestations of GVHD Ophthalmology 1983;90 4-13

69 Yakamoto,Kuwana Successful treatment of dry eye in two patients with chronic GVHD Cornea 200120 430-434

70 Rocha EM, Pelegrino FS, de Pavia : GVHD dry eye treated with autologous serum tears ; Bone marrow transplant 2000 ;25:1101 – 1103

71 Plugfelder SC, Soloman A, Sterne ME ; The diagnosis an management of dry eye – a twenty five year rewiew. Cornea 2000 ;19 644 -49

72 Kono K, Narushima K ; Beneficial effect of local application of plasma fibronectin and autologous serum in patients with keratoconjunctivitis sicca of sjogren's syndrome ; Ryumachi 1986 ;26 339- 343

73 PT, Sivakumaran M, Fahy G – successful use of topical retinoic acid in severe dry eye due to chronic graft – Versus host disease. Bone marrow transplantat 1996 18 641 – 642

74 Ogawa,Sinichiro Okamoto, Masataka Kuwana ; Successful Treatment of Dry eye in two patients with chronic graft versus host disease with systemic administration of FK506 and corticosteroids ;Cornea 2001 20 (4430 – 434

75 Wilson SE Inflammation : A unifying Theory for the origin of dry eye syndrome P&T Digest Dec 2003:28:12

76 Clinical Trail : Cyclosporine implant for ocular Graft –Versus – host clinicaltrials.gov/ct/show/NCT00102583 - 23k –

77 Jacobiec Chapter 335 pages 4999 Graft versus Host Disease

78 Tichelli Cataract formation after bone marrow Transplantation.Ann Int Med 1993 119:1175-1180.

79 Dunn, Jabs Wingard BMT and Cataract Development Arch Ophthal 1367-1373 1993

80 Kerty et al Ocular Findings in Allogenic Stem cell Transplantation without Total Body Irradiation. Ophthalmology Volume 106,Number 7 July 1999

81 Fareher,Kenyon,Tushka Ocular Manifestations of GVHD OPhtal 904-913 1983

82 Jack MK HicksJD Ocular Complications in high dose chemotherapy and marrow transplantation .Ann Qphthal 1981 13 709-11

83 Robinson et al Topical corticosteroid therapy for cicatricial conjunctivitisassociated with chronic GVHDBone Marrow Transplant 2004 33 1031-1035.

84 Sullivan, Deeg, Fluornoy Cataracts after total body irradiation and marrow transplantation. Int J Radiat Onco Biol Phys 1984; 10:957-964

85 Sasaki, Shibata,Obazawa Classification System for cataracts. Application by the Japanese Co operarive Cataract Epidemiological Study Group.Ophthal Res22 (sup)1)46,1990

APPENDIX

APPENDIX

The diagnostic tests for dry eye are the Schirmer test, Tear break up time, Tear meniscus height and tear debris and Fluorescein staining of the cornea.

(1) Schirmer test: Measures the quantity of the tears produced by the eye.[62]

Schirmer Ia: Tests basic and reflex secretions.

A standardized strip of filter paper (Whatman No:41) is placed in the eye. The patient is instructed to look forward and to blink normally during the course of the test. After 5 minutes the filter paper is removed and the length of the moistened part is measured. Less than 5mm of wetting is suggestive of dry eye.

Schirmer Ib :

The same test is done after instilling local anesthetic. This measures mainly the basal secretion. The reflex secretion is not completely abolished by this test. Less than 5mm at 5 minutes is suggestive of dry eye.

(2)Tear break up time

A drop of fluorescein is instilled in the eye, time in seconds between the last blink and the first randomly distributed dry spot is noted under slit lamp with cobalt blue illumination.[63] Ten seconds is the normal cutoff for TBUT.

It is a specific test for mucin deficiency. Limitations are that erratic results occur in the absence of standard conditions and corneal surface irregularities affect accurate measurements.

(3**) Fluorescein staining of the cornea**.

Fluorescein staining manifests where cell to cell junctions are disrupted.[64]t lacks the ability to be blocked by tear constituents and diffuses rapidly into the stroma It acts as a vital stain adhering to devitalized cells. The area and density of staining is measured and graded.

(4) **Tear meniscus**:

Height of less than 0.2mm / presence of debris is suggestive of dry eye.[65]

Various studies have taken one or more of the above tests to diagnose dry eye.

Proforma

Ocular complications in Bone marrow and peripheral blood stem cell transplantation

Hospital number : Schell CMCH

Name Address

DOB Age Sex Male Female

Diagnosis

AML / ALL / CLL / CML
Aplastic anemia
Thalasaemia

Pre BMT conditioning : TBI / Chemotherapy / Both

GVHD Prophylaxis : Cyclosporine + Methotreaxate / Cyclosporine + Methylprednisolone

BMT : Date
Type Allogenic /Syngenic/ Autogenic
PBSC /BMT / CB
Time of engraftment-ANC/platelet count
Systemic complications:

Infections :
Date
Type - fungal / bacterial / viral / parasitic
Investigations – blood culture / urine / pus /CXR / BAL / PCR / clinical/ others
Treatment : antibiotics /antifungals /antiparasitic /
Number of days

GVHD
Present / absent
Time of onset
Acute /chronic / acute on chronic
Clinical features – skin (01234) / liver (01234) /GIT (01234) /
Treatment – Steroids / Cyclosporine /Methotrexate
Investigations – PCV /Hb / MCHC / BP / LFT / PT /PTT Date

OPHTHALMIC EVALUATION

		Pre date		Post I date		Post II date	
		R	L	R	L	R	L
Visual acuity	Unaided						
	BCVA						
	Ref error						
Lids Acute Dermatitis	Erythema						
	Blisters						
	Desquamation						
Chronic Dermatitis	Ectropion						
	Lagopthalmos						
	Scarring						
Dry eye	Tear lake						
	Schirmer test						
	TBUT						
	SPK A/D						
	Thinning						
	Pannus						
	Filaments						
	Ulcer infectious / sterile						
Upper Tarsal Conjunctiva	Hypermia						
	Chemosis						
	Pseudomembrane						
	Epithelial loss						
	Scarring						
Uveitis	Anterior						

	Posterior
	Pan
Pupil	RAPD
	IOP
Cataract	NS I/II/III/IV
	PSC I/II/III
BMT	
Retinopathy	
infections	CMV
	HZ
	Fungal
	Toxo
	Endopthalmitis
Hematologic	VH
	IR Hg
CSR	
ERM	
Others	
Intervention	Nil
	Lubricants
	Cyclosporine
	Punctual occlusion
	Tarrsoraphy
	Others

Examiner's notes:

Ophthalmological diagnosis :